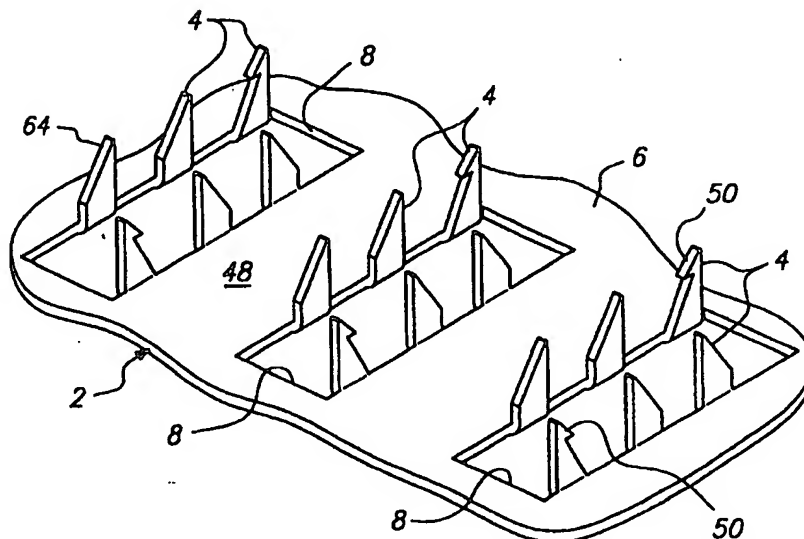




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(54) Title: **DEVICE AND METHOD FOR ENHANCING TRANSDERMAL AGENT FLUX**

## (57) Abstract

An agent delivery or sampling device (2) comprising a member (6) having a plurality of blades (4) for piercing the skin and a connecting medium (65) covering at least a part of the skin contacting side (48) of the member (6) for increasing transdermal flux of an agent.

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1           **DEVICE AND METHOD FOR ENHANCING TRANSDERMAL**  
2                                   **AGENT FLUX**

3  
4  
5                                   **TECHNICAL FIELD**

6  
7           The present invention relates to transdermal agent delivery and  
8 sampling. More particularly, this invention relates to the transdermal  
9 delivery of agents, such as peptides and proteins, through the skin of an  
10 animal, as well as the transdermal sampling of agents, such as glucose,  
11 electrolyte and substances of abuse, such as but not limited to alcohol and  
12 illicit drugs.

13  
14                                   **BACKGROUND ART**

15  
16           Interest in the percutaneous or transdermal delivery of peptides and  
17 proteins to the human body continues to grow with the increasing number  
18 of medically useful peptides and proteins becoming available in large  
19 quantities and pure form. The transdermal delivery of peptides and proteins  
20 still faces significant problems. In many instances, the rate of delivery or  
21 flux of polypeptides through the skin is insufficient to produce a desired  
22 therapeutic effect due to the low flux of polypeptides through skin. In  
23 addition, polypeptides and proteins are easily degradable during and after  
24 penetration of the skin, prior to reaching target cells. Likewise, the passive  
25 flux of water soluble small molecules such as salts is limited.

26           One method of increasing the transdermal delivery of agents relies  
27 on the application of an electric current across the body surface or on  
28 "electrotransport". "Electrotransport" refers generally to the passage of a  
29 beneficial agent, e.g., a drug or drug precursor, through a body surface such  
30 as skin, mucous membranes, nails, and the like. The transport of the agent  
31 is induced or enhanced by the application of an electrical potential, which  
32 results in the application of electric current, which delivers or enhances  
33 delivery of the agent. The electrotransport of agents through a body surface  
34 may be attained in various manners. One widely used electrotransport  
35 process, iontophoresis, involves the electrically induced transport of charged  
36 ions. Electroosmosis, another type of electrotransport process, involves the  
37 movement of a solvent with the agent through a membrane under the  
38 influence of an electric field. Electroporation, still another type of

1 electrotransport, involves the passage of an agent through pores formed by  
2 applying a high voltage electrical pulse to a membrane. In many instances,  
3 more than one of these processes may be occurring simultaneously to  
4 different extents. Accordingly, the term "electrotransport" is given herein its  
5 broadest possible interpretation, to include the electrically induced or  
6 enhanced transport of at least one charged or uncharged agent, or mixtures  
7 thereof, regardless of the specific mechanism(s) by which the agent is  
8 actually being transported. Electrotransport delivery generally increases  
9 agent delivery, particularly peptide delivery rates, relative to passive or non-  
10 electrically assisted transdermal delivery. However, further increases in  
11 transdermal delivery rates and reductions in peptide degradation during  
12 transdermal delivery are highly desirable.

13 One method of increasing the agent transdermal delivery rate  
14 involves pre-treating the skin with, or alternatively co-delivering with the  
15 beneficial agent, a skin permeation enhancer. The term "permeation  
16 enhancer" is broadly used herein to describe a substance which, when  
17 applied to a body surface through which the agent is delivered, enhances its  
18 flux therethrough. The mechanism may involve a reduction of the electrical  
19 resistance of the body surface to the passage of the agent therethrough, an  
20 increase in the permeability of the body surface, the creation of hydrophilic  
21 pathways through the body surface, and/or a reduction in the degradation of  
22 the agent (e.g., degradation by skin enzymes) during electrotransport.

23 There have been many mechanical attempts to enhance transdermal  
24 flux, such as, U. S. Patent Nos. 5,279,544 issued to Gross et al., 5,250,023  
25 issued to Lee et al., and 3,964,482 issued to Gerstel et al. These devices  
26 utilize tubular or cylindrical structures generally, although Gerstel does  
27 disclose the use of other shapes, to pierce the outer layer of the skin.  
28 Each of these devices provide manufacturing challenges, limited mechanical  
29 attachment of the structure to the skin, undesirable irritation to the skin,  
30 and/or limited conductive contact with the skin.

31

## 32 **DESCRIPTION OF THE INVENTION**

33

34 The present invention is a high volume producable, low-cost device  
35 suitable for increasing transdermal flux with skin piercing protrusions and  
36 contacting a body surface over a large contact area to reduce skin irritation  
37 and enhance agent delivery or sampling. The device of the present

1 invention pierces the stratum corneum of a body surface to form pathways  
2 through which a substance can either be introduced (i.e., delivery) or  
3 withdrawn (i.e., sampling). In one aspect, the invention comprises a plurality  
4 of protrusions for piercing the skin which extend through a connecting  
5 medium. The connecting medium assists in making substantial contact  
6 with the body surface for either delivering or sampling an agent. For an  
7 electrotransport device, the connecting medium spreads out the contact  
8 area to all the protrusions to reduce the current density at particular  
9 locations to reduce irritation.

10 In one aspect of the invention, the device utilizes a member having a  
11 plurality of openings therethrough, a plurality of blades integral therewith  
12 and extending downward from a first side of the member, and a connecting  
13 medium covering at least a part of the first side of the member. The device  
14 of the present invention can be used in connection with agent delivery,  
15 agent sampling or both. Delivery devices for use with the present invention  
16 include, but are not limited to, electrotransport devices, passive devices,  
17 osmotic devices and pressure driven devices. Sampling devices for use  
18 with the present invention include, but are not limited to, reverse  
19 electrotransport devices, passive devices, and osmotic devices.

#### 20 21 **BRIEF DESCRIPTION OF THE DRAWINGS**

22  
23 Figure 1 is an enlarged cross-sectional view of a skin piercing device  
24 in accordance with the present invention;

25  
26 Figure 2 is an enlarged perspective view of the bottom side of a skin  
27 piercing device with a connecting medium removed therefrom for clarity in  
28 accordance with one embodiment of the present invention;

29  
30 Figure 3 is a exploded perspective view of one embodiment of an  
31 electrotransport agent delivery system according to one embodiment of the  
32 present invention;

33  
34 Figure 4 is a bottom plan view of the electrotransport agent delivery  
35 system of figure 3;

1           Figure 5 is a right side elevational view of the electrotransport agent  
2 delivery system of figure 3;

3  
4           Figure 6 is a rear elevational view of the electrotransport agent  
5 delivery system of figure 3;

6  
7           Figure 7 is a cross-sectional view taken along line 7-7 of the  
8 assembled electrotransport agent delivery system of figure 5;

9  
10          Figure 8 is a diagrammatic cross-sectional view of a passive agent  
11 delivery system in accordance with one embodiment of the present  
12 invention;

13  
14          Figure 9 is a diagrammatic cross-sectional view of another  
15 embodiment of a passive agent delivery system in accordance with the  
16 present invention; and

17  
18          Figure 10 is a diagrammatic cross-sectional view of an osmotic  
19 sampling system in accordance with one embodiment of the present  
20 invention.

## 21                                   **MODES FOR CARRYING OUT THE INVENTION**

22  
23  
24          Turning now to the drawings in detail, the skin piercing device 2  
25 of the present invention is generally shown in Figure 1. Device 2 is used  
26 for the percutaneous administration or sampling of an agent. The terms  
27 "substance", "agent" and "drug" are used interchangeably herein and  
28 broadly include physiologically or pharmacologically active substances for  
29 producing a localized or systemic effect or effects in mammals including  
30 humans and primates, avians, valuable domestic household, sport or farm  
31 animals, or for administering to laboratory animals such as mice, rats,  
32 guinea pigs, and the like. These terms also include substances such as  
33 glucose, electrolyte, alcohol, illicit drugs, etc. that can be sampled through  
34 the skin. The major barrier properties of the skin, such as resistance to  
35 agent conduction, reside with the outer layer (i.e., stratum corneum). The

1 inner division of the epidermis generally comprises three layers commonly  
2 identified as stratum granulosum, stratum malpighii, and stratum  
3 germinativum. There is essentially little or no resistance to conduction or to  
4 absorption of an agent through the stratum granulosum, stratum malpighii,  
5 and stratum germinativum. The device of the present invention is used to  
6 pierce the stratum corneum for improved delivery or sampling of an agent  
7 and to make contact with the skin over a large contact area using a  
8 connecting medium 65 (FIG. 1).

9 The connecting medium 65 of the present invention is predisposed on  
10 the skin contacting side 48 of the agent delivery or sampling device. In one  
11 embodiment, the connecting medium 65 is a conduit for the agent and acts  
12 as a bridge between the agent containing or collecting reservoir 26 and the  
13 skin, thus allowing an agent to be transported unhindered therethrough.  
14 The connecting medium can be free of agent or preloaded with agent.  
15 In the embodiment of FIG. 1, the reservoir 26 is illustrated as being separate  
16 from the connecting medium 65. It should be appreciated, however, that in  
17 some embodiments there will be migration of agent into the connecting  
18 medium prior to use of the device such that the reservoir and connecting  
19 medium are not discrete, for example, the matrix in the reservoir and the  
20 connecting medium can be the same material. In addition, a separate  
21 reservoir may not be present in that the connecting medium 65 may be the  
22 reservoir for the sampled agent or the agent to be delivered. In other words,  
23 the connecting medium is capable of storing the agent to be delivered or the  
24 sampled agent.

25 The connecting medium 65 is either fabricated and stored dry which  
26 can be rehydrated upon use or can be packaged in the hydrated form.  
27 In a preferred embodiment, the connecting medium is an ion conducting  
28 hydrogel of a pharmaceutically acceptable grade with minimum extractable  
29 or degradation products which sorbs or contains in a functional state an  
30 amount of water in the range from 20% to 90%, preferably in the range from  
31 30% to 70%. Preferably the connecting medium is a hydrogel that is at least

1 slightly crosslinked to prevent fragments of polymers from penetrating the  
2 skin and has adhesive or tacky properties.

3 The connecting medium 65 can be any of a large variety of materials  
4 as discussed above and further including, by way of example, an organic  
5 polymer having at least some pendent substituents capable of being ionic,  
6 a polar natural material, a semi-synthetic material, a cellulosic derivative,  
7 an alginate derivative, a starch derivative, a dextran, a polysaccharide,  
8 a hydrogel polymer having a backbone selected from the group consisting  
9 of a hydrous-gelled, linear polyolefin, polycarbonate, polyester, polyether,  
10 polyurethane and polyepoxide backbone, with backbone substituents  
11 selected from the group consisting of (alkyl, aryl or aralkyl) alcohol, amide,  
12 ketone, nitrogen heterocycle or ester pendent substituents, and any  
13 combination thereof. The connecting medium can be in a variety of forms  
14 such as a gel, solid, hydrogel, powder, liquid, viscous fluid, gauze made of  
15 cotton or other absorbent fabrics as well as pads and sponges, both natural  
16 and synthetic, may be used. Any suitable materials listed in U.S. Patent  
17 No. 5,385,543 could be used in conjunction with the present invention.  
18 U.S. Patent No. 5,423,739, issued to Phipps et al., describes iontophoretic  
19 materials and substances that can be used as the connecting medium.

20 Device 2 comprises a plurality of protrusions 4 extending downward  
21 from one surface of a member or plate 6 which has a connecting medium 65  
22 (FIG. 1) on at least a portion of surface 48 (see Figure 2 in which device 2 is  
23 in an inverted position to show the protrusions and wherein the connecting  
24 medium is removed for clarity). The protrusions 4 can be blades (FIGS. 1  
25 and 2), pins (not shown), or any of a variety of configurations for piercing the  
26 skin or body surface. The protrusions 4 penetrate the stratum corneum of  
27 the epidermis when pressure is applied to the device to increase the  
28 administration of or sampling of a substance through a body surface.  
29 The term "body surface" as used herein refers generally to the skin,  
30 mucous membranes, and nails of an animal or human, and to the outer  
31 surface of a plant. The protrusions 4 extend through the connecting medium



1 65 to pierce the body surface to create good agent conduction from the  
2 system into the body, or vice versa. The member 6 is formed with an  
3 opening 8 between the blades 4 for enhancing the movement of agent  
4 released from or collected in the agent containing or collecting reservoir 26.  
5 In one embodiment, the opening 8 corresponds to the portion of the member  
6 occupied by each of the blades 4 prior to the blades being bent into a  
7 position which is substantially perpendicular to the plane of member 6.  
8 The number of openings per device and the number of blades per device  
9 are independent. In addition, the device may have only one large opening  
10 with a plurality of blades around the opening. The agent can be  
11 administered or sampled at a controlled rate of release from or collection in  
12 the reservoir 26 through an agent rate controlling material such as a flux  
13 control membrane (not shown) positioned between the reservoir 26 and the  
14 member 6.

15 The protrusions or blades 4 are generally formed from a single piece  
16 of material and are sufficiently sharp and long for puncturing at least the  
17 stratum corneum of the skin. In one embodiment, the blades 4 and the  
18 member 6 are essentially impermeable or are impermeable to the passage  
19 of an agent. The width of each blade can be any of a range of widths.  
20 The blades 4 can have slanted (i.e., angled) leading edges 64 (FIG. 2) to  
21 further reduce the insertion force required to press the blades into the skin  
22 tissue. The leading edges of each blade can be all be the same angle or  
23 can be at different angles suitable for piercing the skin. Alternatively, the  
24 leading edge of each blade can be arcuate (i.e., curved) in shape, having,  
25 for example, a convex or concave shape.

26 The device 2 of the present invention improves the attachment of the  
27 device to the skin so that a continuous agent conducting pathway through  
28 the body surface is preserved during movement of the body surface. In the  
29 embodiment shown in Figure 2, projections in the form of barbs 50 on at  
30 least one of the blades 4 assist in anchoring the device 2 and any  
31 corresponding device or structure used in combination therewith to the skin.

1   Barbs 50 can be on any number of the blades from one blade to all blades.  
2   The barbs 50 are optional as other means for holding the device in contact  
3   with the skin can be used. The present invention can be used in conjunction  
4   with a wide variety of blade configurations, for example reference may be  
5   had to U.S. Provisional Application No. 60/019,990 filed June 18, 1996 of  
6   which any of the disclosed configurations can be used with the present  
7   invention.

8           The pattern for any of the blade array devices 2 of the present  
9   invention can be produced with a photo-etching process. A thin member 6  
10   of metal such as stainless steel or titanium is etched photo-lithographically  
11   with patterns containing blade-like structures. In general, a thin laminate dry  
12   resist or wet resist is applied on the member 6 which typically has a  
13   thickness of about 7 micrometers to about 100 micrometers, preferably  
14   about 25 micrometers to about 50 micrometers. The resist is contact  
15   exposed using a mask having the desired pattern and is subsequently  
16   developed. These operations are conducted in much the same way that  
17   they are for the manufacture of a printed circuit board. The member 6 is  
18   then etched using acidic solutions. After the pattern has been etched  
19   through the member, the member 6 is placed on a die having a plurality of  
20   openings corresponding to the openings 8 in the member. A punch having a  
21   plurality of protrusions corresponding to the openings 8 in the member 6 and  
22   openings in the die is initially located above the member and the die. At the  
23   initial stage, the blades 4 are in the same plane as the rest of the member 6.  
24   The protrusions on the punch are then pressed into the openings, thus  
25   bending the blades downward to be substantially perpendicular to the plane  
26   of the member 6. The finished structure provides blades 4 with an adjacent  
27   opening 8 for the passage of a substance therethrough when the device 2 is  
28   applied to the body surface. Rectangular openings 8 are shown in the  
29   figures but the invention encompasses the use of any shape openings  
30   including, but not limited to, square, triangular, circular and elliptical.

1           In one embodiment of the etching process, a dry resist (e.g.,  
2 "Dynachem FL" available from Dynachem located in Tustin, CA is applied  
3 12.5 micrometers thick to one or both sides of the member 6 and exposed in  
4 a standard manner. Then using a suitable spray etcher (e.g., "Dynamil VRP  
5 10/NM" available from Western Tech. Assoc. located in Anaheim, CA) a  
6 mixture of ferric chloride and hydrochloric acid is sprayed onto the resist and  
7 member 6 at 125 degrees F for two minutes. A standard caustic stripper is  
8 used for the resist removal.

9           In another embodiment of the etching process, a wet resist (e.g.,  
10 "Shipley 111S" available from Shipley Corporation, located in Marlborough,  
11 MA) is applied 7.5 micrometers thick at about 70 degrees F to one or both  
12 sides of the member 6 and exposed in a standard manner. Then a suitable  
13 etchant (e.g., ferric chloride) is sprayed onto the resist and member at  
14 120 degrees F. A standard caustic stripper is used for the resist removal.

15           Generally, the blades 4 are at an angle of about 90 degrees to the  
16 surface 48 of the member 6 after being punched, but they can be disposed  
17 at any angle forward or backward from the perpendicular position that will  
18 facilitate penetration of and attachment to the stratum corneum. In addition,  
19 other anchoring elements such as barbs, openings, etc. can be used with  
20 the angled blades to further enhance anchoring of the device.

21           The member 6 and blades 4 can be made from materials that have  
22 sufficient strength and manufacturability to produce blades, such as,  
23 glasses, ceramics, rigid polymers, metals and metal alloys. Examples of  
24 metals and metal alloys include but are not limited to stainless steel, iron,  
25 steel, tin, zinc, copper, silver, platinum, aluminum, germanium, nickel,  
26 zirconium, titanium and titanium alloys having nickel, molybdenum or  
27 chromium. Each of the member and blades can have a thin layer of silver,  
28 gold, platinum, iridium, titanium, rhodium plating or evaporated or sputtered  
29 biocompatible metals to provide for inertness, biocompatibility and  
30 preservation of the sharpness of the edges during storage. An example of  
31 glasses include a devitrified glass such as "Photoceram" available from  
32 Corning in Corning, NY. Examples of polymers include but are not limited  
33 to polystyrene, polymethylmethacrylate, polypropylene, "Bakelite",  
34 celluloseacetate, ethylcellulose, styrene/acrylonitrile copolymers,  
35 styrene/butadiene copolymers, acrylonitrile/butadiene/styrene (ABS)

1 copolymers, polyvinyl chloride and acrylic acid polymers including  
2 polyacrylates and polymethacrylates.

3 The number of blades 4 and openings 8 of any of the embodiments  
4 of the device 2 is variable with respect to the desired flux rate,  
5 agent being sampled or delivered, delivery or sampling device used  
6 (i.e., electrotransport, passive, osmotic, pressure driven, etc.), and  
7 other factors as will be evident to one of ordinary skill in the art.  
8 In general, the larger the number of blades per unit area (i.e., blade density),  
9 the more uniform the flux of the agent is through the skin because there are  
10 a greater number of pathways through the skin. Consequently, the smaller  
11 the number of blades per unit area, the more concentrated the flux of the  
12 agent is through the skin because there are fewer pathways. Higher  
13 concentrations of agents in a skin pathway typically lead to higher  
14 incidences and/or severity of skin reactions (e.g., irritation). Therefore,  
15 larger blade densities reduce the incidence and/or severity of skin reactions.

16 One embodiment of the present invention relies on the application of  
17 an electric current across the body surface or "electrotransport". It will be  
18 appreciated by those working in the field that the present invention can  
19 be used in conjunction with a wide variety of electrotransport systems,  
20 as the invention is not limited in any way in this regard. For examples  
21 of electrotransport systems, reference may be had to U.S. Patent  
22 Nos. 5,147,296 to Theeuwes et al., 5,080,646 to Theeuwes et al., 5,169,382  
23 to Theeuwes et al., 5,423,739 to Phipps et al., 5,385,543 to Haak et al.,  
24 5,310,404 to Gyory et al., and 5,169,383 to Gyory et al., of which any of the  
25 disclosed electrotransport systems can be used with the present invention.

26 Figures 3-7 illustrate a representative electrotransport delivery device  
27 10 that may be used in conjunction with the present invention. Device 10  
28 comprises an upper housing 16, a circuit board assembly 18, a lower  
29 housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26,  
30 cathode reservoir 28 and skin-compatible adhesive 30. Upper housing 16  
31 has lateral wings 15 which assist in holding device 10 on a patient's skin.  
32 Printed circuit board assembly 18 comprises an integrated circuit 19 coupled  
33 to discrete components 40 and battery 32. Circuit board assembly 18 is  
34 attached to housing 16 by posts (not shown in Figure 3) passing through  
35 openings 13a and 13b, the ends of the posts being heated/melted in order  
36 to heat stake the circuit board assembly 18 to the housing 16. Lower  
37 housing 20 is attached to the upper housing 16 by means of adhesive layer

1 30, the upper surface 34 of adhesive layer 30 being adhered to both lower  
2 housing 20 and upper housing 16 including the bottom surfaces of wings 15.  
3 Shown (partially) on the underside of circuit board assembly 18 is a button  
4 cell battery 32. Other types of batteries may also be employed to power  
5 device 10 depending on the need.

6 The device 10 is generally comprised of battery 32, electronic circuitry  
7 19,40, electrodes 22,24, agent reservoirs 26,28, and skin piercing device 2,  
8 all of which are integrated into a self-contained unit. Electrodes 22,24 and  
9 reservoirs 26,28 are retained by lower housing 20. Anodic electrode 22 is  
10 preferably comprised of a metal such as silver and cathodic electrode 24 is  
11 preferably comprised of a metal halide such as silver chloride. The outputs  
12 (not shown in Figure 3) of the circuit board assembly 18 make electrical  
13 contact with the electrodes 24 and 22 through openings 23,23' in the  
14 depressions 25,25' formed in lower housing 20, by means of electrically  
15 conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn, are in  
16 direct mechanical and electrical contact with the top sides 44',44 of agent  
17 reservoirs 26 and 28. The bottom side 46 of agent reservoir 28 contacts the  
18 patient's skin through the opening 29 in adhesive layer 30. The bottom side  
19 46' of agent reservoir 26 contacts the connecting medium through the  
20 plurality of openings 8 in the skin piercing device 2. The agent in reservoir  
21 26 is typically a viscous gel that fills the openings 8 such that the agent  
22 reservoir is in contact with the connecting medium 65 as can be seen in FIG.  
23 1. As discussed above, typically the agent is present initially in both the  
24 reservoir and the connecting medium because of diffusion or because the  
25 reservoir and connecting medium are the same material. Both reservoirs 26  
26 and 28 are preferably comprised of polymeric gel materials. A liquid agent  
27 solution or suspension is contained in at least one of the reservoirs 26  
28 and 28.

29 The device 10 adheres to the patient's body surface (e.g., skin) by  
30 means of an adhesive layer 30 (which has upper adhesive side 34 and  
31 body-contacting adhesive side 36) and, optionally, anchoring elements on  
32 the device 2 of any of the embodiments discussed herein. Further,  
33 optionally, the connecting medium 65 can be tacky or adhesive for assisting  
34 in maintaining contact with the skin. The adhesive side 36 covers the entire  
35 underneath side of the device 10 except where the device 2 and cathodic  
36 electrode are located. The adhesive side 36 has adhesive properties which

1 assures that the device 10 remains in place on the body during normal user  
2 activity, and yet permits reasonable removal after the predetermined  
3 (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower  
4 housing 20 and retains the electrodes and agent reservoirs within housing  
5 depression 25, 25' as well as retains device 2 to lower housing 20 and lower  
6 housing 20 to upper housing 16.

7 In one embodiment of the agent delivery device there is a release  
8 liner (not shown) on the device 10 for maintaining the integrity of the device  
9 when it is not in use. In use, the release liner is stripped from the device  
10 before the device is applied to the skin. Device 10 also has a push button  
11 switch 12, which when pressed turns the device 10 on which is made  
12 apparent to the user by means of LED 14 becoming lit. Drug is delivered  
13 through the patient's skin (e.g., on the arm) by electrotransport over the  
14 predetermined delivery interval.

15 Examples of neutral or uncharged hydrogels for use in the  
16 electrotransport system are polyvinyl alcohol crosslinked through a heating  
17 or cooling crystallization process or a combination of polyox crosslinked with  
18 carbopol or polyacrylic acid. The connecting medium can be electrically  
19 charged such as an ion exchange resin with a fixed charge and mobile  
20 counter charges. A preferred embodiment is a resin with fixed charges  
21 opposite the charge of the agent ion. An example of an ionically charged or  
22 ion exchange resin is cholestyramine®.

23 In other embodiments of the present invention, passive transdermal  
24 delivery or sampling devices are used with a connecting medium 65  
25 predisposed on the bottom (i.e., skin facing) surface of the device. It will be  
26 appreciated by those working in the field that the present invention can be  
27 used in conjunction with a wide variety of passive transdermal systems, as  
28 the invention is not limited in this regard. For examples of passive systems,  
29 reference may be had to, but not limited to, U.S. Patent Nos. 4,379,454 to  
30 Campbell et al., 4,588,580 to Gale et al., 4,832,953 to Campbell et al.,  
31 4,698,062 to Gale et al., 4,867,982 to Campbell et al., and 5,268,209 to  
32 Hunt et al., of which any of the disclosed systems can be used with the  
33 present invention. Two examples of passive transdermal delivery devices  
34 are illustrated in Figures 8 and 9.

35 In Figure 8, passive transdermal delivery device 88 comprises a  
36 reservoir 90 containing a therapeutic agent (e.g., a drug) to be delivered  
37 transdermally. Reservoir 90 is preferably in the form of a matrix containing

1 the agent dispersed therein. Reservoir 90 is sandwiched between a backing  
2 layer 92, which is impermeable to the agent, and an optional rate-controlling  
3 membrane 94. In Figure 8, the reservoir 90 is formed of a material, such as  
4 a polymer, that is sufficiently viscous to maintain its shape. If a lower  
5 viscosity material is used for reservoir 90, such as an aqueous gel, backing  
6 layer 92 and rate-controlling membrane 94 would be sealed together about  
7 their periphery to prevent leakage. Located below membrane 94 is skin  
8 piercing device 2 with connecting medium 65 on a skin facing surface  
9 thereof which extends through the openings (not shown) in device 2 to  
10 contact membrane 94. The device 88 adheres to a body surface by means  
11 of contact adhesive layer 96 around the periphery of the device 2 and,  
12 optionally, by the anchoring elements of any of the embodiments described  
13 previously. In most instances, the connecting medium 65 will initially contain  
14 agent. A strippable release liner (not shown) is normally provided along the  
15 exposed surface of adhesive layer 96 and is removed prior to application of  
16 device 10 to the body surface.

17 Alternatively, as shown in enlarged Figure 9, transdermal therapeutic  
18 device 98 may be attached to a body surface by means of a flexible  
19 adhesive overlay 100. Device 98 is comprised of an agent-containing  
20 reservoir 90 which is preferably in the form of a matrix containing the agent  
21 dispersed therein. Connecting medium 65 extends through the openings 8  
22 to contact the reservoir 90. Alternatively, the matrix in reservoir 90 can  
23 extend through the openings 8 initially to be in contact with the connecting  
24 medium 65 or the reservoir and connecting medium can be the same.  
25 An impermeable backing layer 102 is provided adjacent one surface of  
26 reservoir 90. Adhesive overlay 100 maintains the device on the body  
27 surface. Adhesive overlay 100 can be fabricated together with, or provided  
28 separately from, the remaining elements of the device 98. With certain  
29 formulations, the adhesive overlay 100 may be preferable to the contact  
30 adhesive 96 shown in Figure 8. This is true, for example, where the agent  
31 reservoir contains a material (such as, for example, an oily surfactant) which  
32 adversely affects the adhesive properties of the contact adhesive layer 96.  
33 Impermeable backing layer 102 is preferably slightly larger than reservoir 90,  
34 and in this manner prevents the agents in reservoir 90 from adversely  
35 interacting with the adhesive in overlay 100. Optionally, a rate-controlling  
36 membrane (not shown in Figure 9) similar to membrane 94 in Figure 8 can  
37 be provided on the body surface side of reservoir 90. A strippable release

1 liner (not shown) is also normally provided with device 98 and is removed  
2 just prior to application of device 98 to the body surface.

3 The formulation of reservoir 90 may be aqueous or nonaqueous  
4 based. The formulation is designed to deliver the agent at the necessary  
5 fluxes. Aqueous formulations typically comprise water and about 1 to 60  
6 weight percent of a hydrophilic polymer as a gelling agent, such as  
7 hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethacrylate  
8 and polymers used in soft contact lenses. Typical non-aqueous  
9 formulations are comprised of silicone fluid, silicone rubbers, hydrocarbon  
10 polymers, polyisobutylene, rubbers, or mineral oil. Mineral oil-based gels  
11 also typically contain 1 to 2 weight percent of a gelling agent such as  
12 colloidal silicon dioxide.

13 The reservoir matrix having agent therein should be compatible with  
14 the delivered agent, uptake inhibiting agent (if any) and any carrier  
15 therefore. When using an aqueous-based system, the reservoir matrix is  
16 preferably a hydrophilic polymer (e.g., a hydrogel). When using a non-  
17 aqueous-based system, the reservoir matrix is preferably composed of a  
18 hydrophobic polymer. Suitable polymeric matrices are well known in the  
19 transdermal drug delivery art.

20 When a constant agent delivery rate is desired, the agent is present  
21 in the matrix or carrier at a concentration in excess of saturation, the amount  
22 of excess being a function of the desired length of the agent delivery period  
23 of the system. The agent may, however, be present at a level below  
24 saturation without departing from this invention as long as the agent and the  
25 uptake-inhibiting agent (if any) are continuously and co-extensively  
26 administered to the same body surface site in an amount and for a period of  
27 time sufficient to reduce or eliminate skin irritation by the agent.

28 In addition to the agent, the connecting medium may also contain  
29 dyes, pigments, inert fillers, permeation enhancers, excipients tackifiers,  
30 neutral polymers, surfactants, reagents, buffers, plasticizers, and other  
31 conventional components of pharmaceutical products or transdermal  
32 devices known in the art.

33 The amount of agent present in the reservoir and the size of the  
34 reservoir is generally non-limited and is an amount equal to or larger than  
35 the amount of agent that in its released form is effective in bringing about  
36 the desired local and/or systemic physiological and/or pharmacological  
37 effects.



1           The preferred form in which an agent is delivered generally  
2 determines the type of delivery system to be used, and vice versa. That is,  
3 the selection of a "passive" system which delivers the agent by diffusion or  
4 an electrically powered system which delivers the agent by electrotransport  
5 will be mostly determined by the form of the agent. For example, with  
6 passive delivery systems, it has generally been recognized that the agent is  
7 preferably delivered in either its free base or acid form, rather than in the  
8 form of a water soluble salt when the agent diffuses through the stratum  
9 corneum. On the other hand, with electrotransport delivery devices, it has  
10 been recognized that the agents should generally be soluble in water. It is  
11 generally believed that the pathways for passive and electrotransported  
12 transdermal agent delivery through intact skin are different, with passive  
13 delivery occurring through lipid regions (i.e., hydrophobic regions) of the skin  
14 and electrotransport delivery occurring through hydrophilic pathways or  
15 pores such as those associated with hair follicles and sweat glands. For the  
16 case of pierced skin, substantial passive flux through the created pathways  
17 which are aqueous can be expected. The agent for passive delivery in the  
18 case of pierced skin is generally hydrophilic (e.g., water soluble salt form)  
19 and the preferred form of an agent for electrotransport delivery is also  
20 hydrophilic (e.g., water soluble salt form). For passive delivery, a  
21 combination of ionized agent (e.g., water soluble) and unionized agent  
22 (e.g., hydrophilic) can be used.

23           For osmotic and pressure driven systems which deliver agents by  
24 connective flow carried by a solvent, the agent preferably has sufficient  
25 solubility in the carrier solvent. It will be appreciated by those working in the  
26 field that the present invention can be used in conjunction with a wide  
27 variety of osmotic and pressure driven systems, as the invention is not  
28 limited to a particular device in this regard. For examples of osmotic and  
29 pressure driven devices, reference may be had to U.S. Patent Nos.  
30 4,340,480 to Eckenhoff, 4,655,766 to Theeuwes et al., 4,753,651 to  
31 Eckenhoff, 5,279,544 to Gross et al., 4,655,766 to Theeuwes, 5,242,406 to  
32 Gross et al., and 4,753,651 to Eckenhoff any of which can be used with the  
33 present invention.

34           This invention has utility in connection with the delivery of agents  
35 within any of the broad class of drugs normally delivered through body  
36 surfaces and membranes, including skin. In general, this includes drugs in  
37 all of the major therapeutic areas including, but not limited to, anti-infectives

1 such as antibiotics and antiviral agents, analgesics including fentanyl,  
2 sufentanil, buprenorphine and analgesic combinations, anesthetics,  
3 anorexics, antiarthritics, antiasthmatic agents such as terbutaline,  
4 anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals,  
5 antihistamines, anti-inflammatory agents, antimigraine preparations,  
6 antinotion sickness preparations such as scopolamine and ondansetron,  
7 antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics,  
8 antipsychotics, antipyretics, antispasmodics, including gastrointestinal and  
9 urinary anticholinergics, sympathomimetics, xanthine derivatives,  
10 cardiovascular preparations including calcium channel blockers such as  
11 nifedipine, beta-blockers, beta-agonists such as dobutamine and ritodrine,  
12 antiarrhythmics, antihypertensives such as atenolol, ACE inhibitors such as  
13 ranitidine, diuretics, vasodilators, including general, coronary, peripheral and  
14 cerebral, central nervous system stimulants, cough and cold preparations,  
15 decongestants, diagnostics, hormones such as parathyroid hormone,  
16 bisphosphonates, hypnotics, immunosuppressives, muscle relaxants,  
17 parasympatholytics, parasympathomimetics, prostaglandins,  
18 psychostimulants, sedatives and tranquilizers.

19 The invention is also useful in the transdermal delivery of proteins,  
20 peptides and fragments thereof, whether naturally occurring, chemically  
21 synthesized or recombinantly produced. The invention may additionally be  
22 used in conjunction with the delivery of nucleotidic drugs, including  
23 oligonucleotide drugs, polynucleotide drugs, and genes. These substances  
24 typically have a molecular weight of at least about 300 daltons, and more  
25 typically have a molecular weight of at least about 300 to 40,000 daltons.  
26 Specific examples of peptides and proteins in this size range include,  
27 without limitation, LHRH, LHRH analogs such as goserelin, buserelin,  
28 gonadorelin, napharelin and leuprolide, GHRH, GHRF, insulin, insulotropin,  
29 calcitonin, octreotide, endorphin, TRH, NT-36 (chemical name: N-[(s)-4-  
30 oxo-2-azetidiny]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary  
31 hormones (e.g., HGH, HMG, desmopressin acetate, etc), follicle luteoids,  
32 ANF, growth factors such as growth factor releasing factor (GFRF), MSH,  
33 GH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor,  
34 asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic  
35 gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol (platelet  
36 aggregation inhibitor), glucagon, HCG, hirulog, hyaluronidase, interferon,  
37 interleukins, menotropins (urofollitropin (FSH) and LH), oxytocin,

1 streptokinase, tissue plasminogen activator, urokinase, vasopressin,  
2 desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II  
3 antagonists, antidiuretic hormone agonists, bradykinin antagonists,  
4 ceredase, CSI's, calcitonin gene related peptide (CGRP), enkephalins,  
5 FAB fragments, IgE peptide suppressors, IGF-1, neurotrophic factors,  
6 colony stimulating factors, parathyroid hormone and agonists, parathyroid  
7 hormone antagonists, prostaglandin antagonists, pentigetide, protein C,  
8 protein S, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines,  
9 vasopressin antagonists analogs, alpha-1 antitrypsin (recombinant), and  
10 TGF-beta.

11 As mentioned, the device 2 of the present invention can also be used  
12 with sampling devices including, but not limited to, reverse electrotransport  
13 (i.e., iontophoresis and/or electroosmosis), osmosis, and passive diffusion.  
14 Figure 10 illustrates an osmotic sampling device 104 in combination with any  
15 of the embodiments described previously for device 2 with connecting  
16 medium 65. Osmotic sampling devices can be used to sample any of a  
17 variety of agents through a body surface including, but not limited to  
18 glucose, electrolyte, alcohol and illicit substances (e.g., drugs of abuse).  
19 The osmotic sampling device 104 is attached to a body surface by means of  
20 a flexible adhesive overlay 100. Device 104 is comprised of a salt layer 106  
21 separated by semi-permeable membrane 95 from a layer 94 which stores  
22 the agent to be sampled. The layer 94 is absorbant in character in that the  
23 layer (e.g., hydrogel) passes fluid drawn through the body surface but  
24 retains the agent being sampled. The device 2 with connecting medium 65  
25 thereon is in contact with layer 94 such that the projections on device 2  
26 pierce the body surface and the connecting medium 65 makes good contact  
27 with the body surface. The salt layer 106 draws fluid from the body by  
28 osmosis through the connecting medium 65 and layer 94. The fluid drawn  
29 from the body contains the agent being sampled. As the fluid containing the  
30 agent passes through layer 94, the agent is retained in layer 94 and the fluid  
31 is absorbed by the salt layer 106. Preferably, the salt layer is free to expand  
32 or is encapsulated in a semi-permeable membrane 95 so that it retains the  
33 fluid therein. The sampled agent can be measured in situ directly or  
34 withdrawn from the layer 94 and sampled by conventional means.

1           Alternatively, salt layer 106, layer 94 and semi-permeable membrane  
2   95 can be combined in one layer of absorbant hydrogel that stores the  
3   absorbed fluid as well as the agent sampled. Additionally, this one layer can  
4   be configured as the connecting medium 65 thereby greatly simplifying the  
5   device.

6           The following example is merely illustrative of the present invention  
7   and should not be considered as limiting the scope of the invention in any  
8   way, as this example and other equivalents thereof will become apparent to  
9   those versed in the art and in light of the present disclosure, drawings, and  
10   the accompanying claims.

11

12

### Example 1

13           The effect of the present invention is evaluated for its effect on drug  
14   flux and the skin resistance of a hairless guinea pig during electrotransport  
15   delivery of a model decapeptide drug. The following are specifications for  
16   the device. The device consists of a member having a plurality of  
17   rectangular openings having two blades, one on each end of a 0.25 mm<sup>2</sup>  
18   void area for each opening. The openings are aligned in pairs with every  
19   other pair of openings oriented 90 degrees to the previous pair of openings.  
20   All of the blades are about 500 micrometers long. There are 256 void areas  
21   per cm<sup>2</sup> and 512 blades per cm<sup>2</sup>. An electrotransport system is used which  
22   applies a constant current of 0.1 mA/cm<sup>2</sup>. It consists of a cathode counter  
23   reservoir comprising a Dulbelco's phosphate buffered saline imbibing gel  
24   and a donor anode reservoir comprising a hydroxyethylcellulose gel  
25   containing an aqueous solution of decapeptide buffered at pH 7.5. The  
26   electrotransport system is placed on the skin of a lightly anesthetized  
27   hairless guinea pig. Decapeptide flux is evaluated by measuring urinary  
28   excretion of this peptide. Use of the present invention results in increased  
29   decapeptide flux over the transport period compared to an ordinary  
30   electrotransport device.

31           It will be appreciated by those of ordinary skill in the art that the  
32   invention can be embodied in other specific forms without departing from the  
33   spirit or essential character thereof. The presently disclosed embodiments  
34   are therefore considered in all respects to be illustrative and not restrictive.  
35   The scope of the invention is indicated by the appended claims rather than  
36   the foregoing description, and all changes which come within the meaning  
37   and range of equivalents thereof are intended to be embraced therein.

## 1 CLAIMS:

2

3 1. A device for introducing or withdrawing an agent through a body  
4 surface, comprising:

5 a member having a plurality of protrusions extending from a body  
6 surface contacting side of the member; and

7 a connecting medium capable of storing the agent therein or passing  
8 the agent therethrough on at least a portion of the body surface contacting  
9 side of the member.

10

11 2. The device of Claim 1 wherein the member has an opening  
12 therethrough.

13

14 3. The device of Claim 2 wherein the connecting medium extends  
15 across the opening.

16

17 4. The device of Claim 2 wherein the connecting medium extends  
18 through the opening.

19

20 5. The device of Claim 2 wherein the connecting medium is in the  
21 opening.

22

23 6. The device of Claim 1 wherein the connecting medium is in the range  
24 of about 10 micrometers to about 100 micrometers thick.

25

26 7. The device of Claim 1 wherein the connecting medium is about 50  
27 micrometers thick.

28

29 8. The device of Claim 1 wherein the connecting medium comprises a  
30 hydrogel.

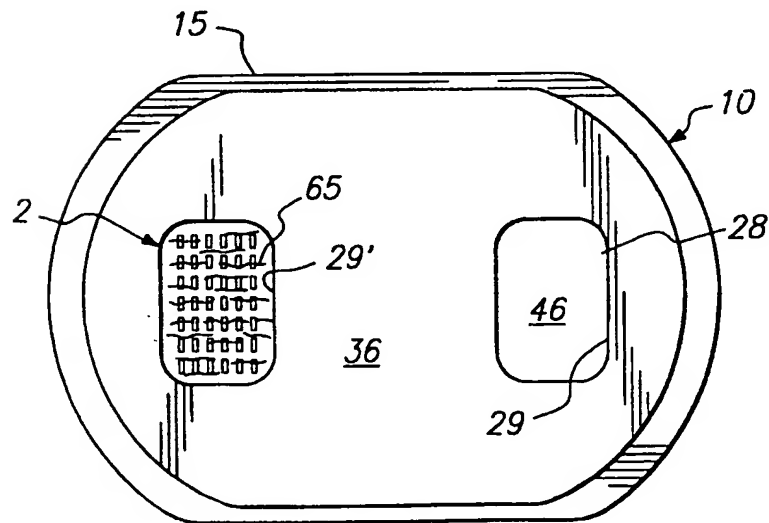
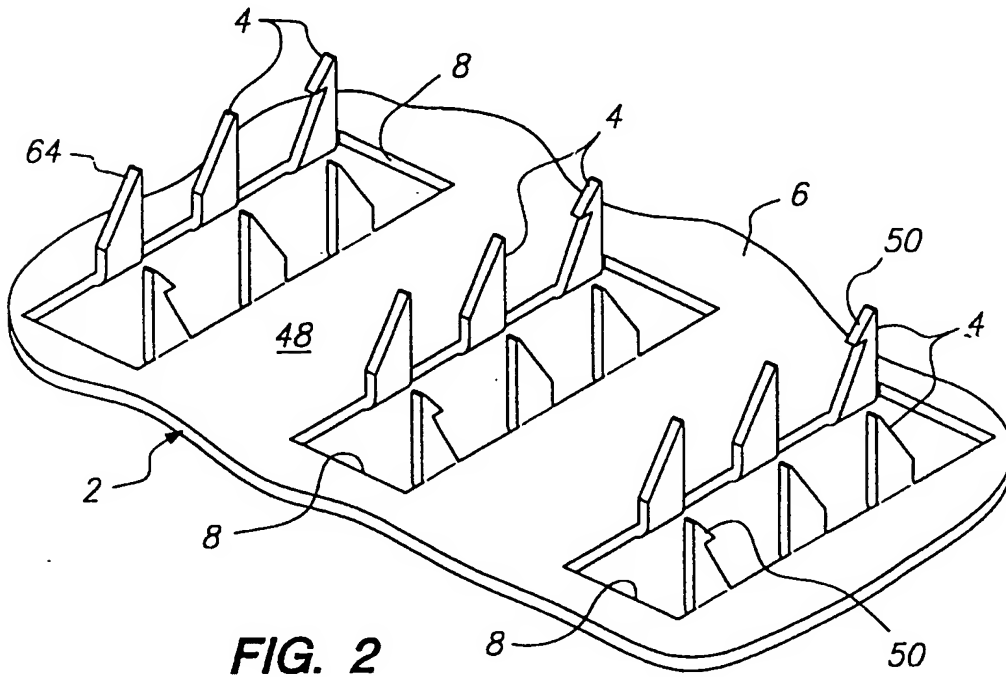
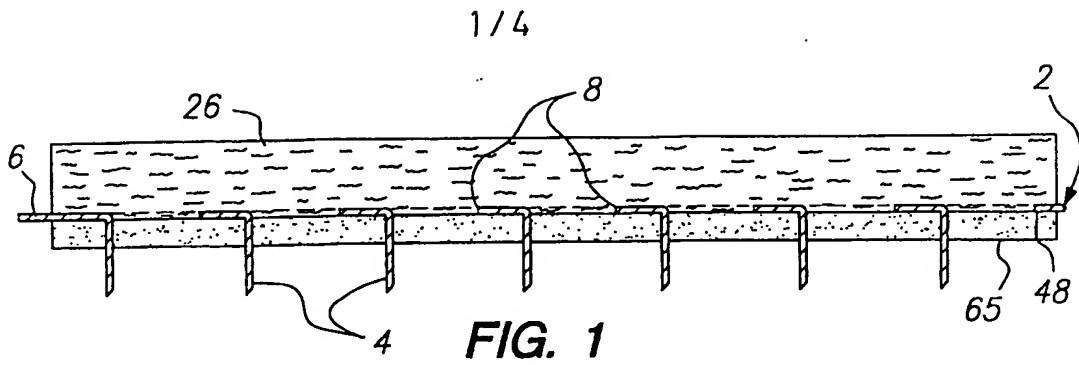
31 9. The device of Claim 1 wherein the connecting medium is preloaded  
32 with the agent to be delivered through the body surface.

33

34 10. The device of Claim 1 wherein the connecting medium comprises a  
35 form selected from the group consisting of a gel, a solid and a powder.

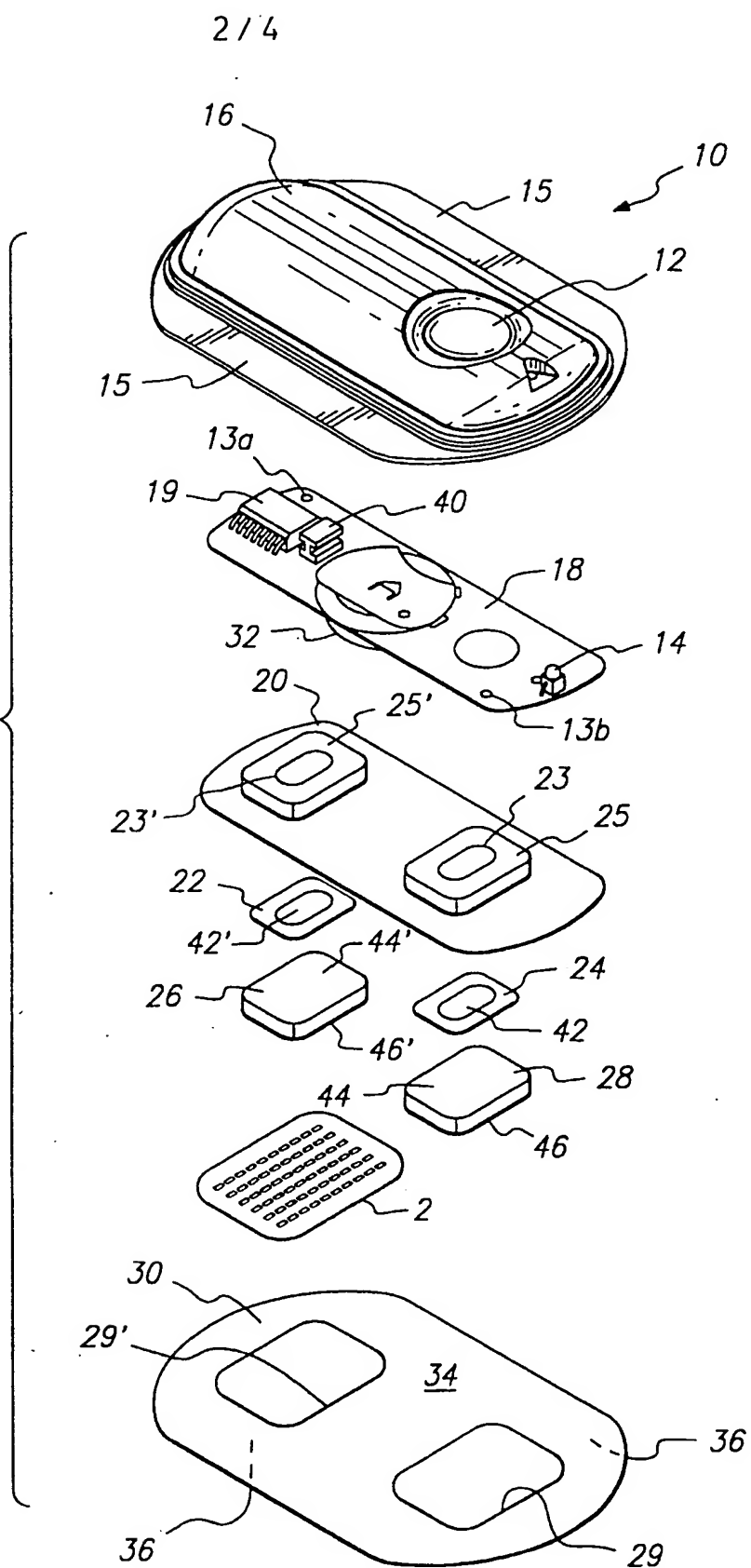
- 1 11. The device of Claim 1 wherein the connecting medium further  
2 comprises a matrix material.  
3
- 4 12. The device of Claim 1 wherein the protrusions comprise blades.  
5
- 6 13. The device of Claim 12 wherein at least one of the plurality of blades  
7 comprises means for anchoring the device to the body surface.  
8
- 9 14. The device of Claim 1 further comprising an agent delivery device  
10 connected to a second side of the member, the agent delivery device  
11 selected from the group consisting of an electrotransport device, a passive  
12 device, an osmotic device, and a pressure driven device.  
13
- 14 15. The device of Claim 14 wherein the agent is selected from the group  
15 consisting of a gene, a polypeptide, and a protein.  
16
- 17 16. The device of Claim 1 further comprising a sampling device  
18 connected to a second side of the member, the sampling device selected  
19 from the group consisting of a reverse electrotransport device, a passive  
20 device, and an osmotic device.  
21
- 22 17. The device of Claim 16 wherein a sampled agent is selected from the  
23 group consisting of body electrolytes, illicit drugs and glucose.  
24
- 25 18. A device for introducing or withdrawing an agent through a body  
26 surface, the device comprising:  
27 a plurality of protrusions extending from a first side and an opening  
28 through the device between the protrusions; and  
29 a connecting medium capable of storing the agent therein or passing  
30 the agent therethrough being predisposed in the opening.  
31
- 32 19. The device of Claim 18 wherein the connecting medium is  
33 predisposed on a portion of the first side.  
34
- 35 20. The device of Claim 18 wherein the agent is selected from the group  
36 consisting of a gene, a polypeptide, and a protein.

- 1 21. The device of Claim 18 wherein the connecting medium comprises a  
2 hydrogel.  
3
- 4 22. The device of Claim 18 wherein the connecting medium is preloaded  
5 with an agent to be delivered through the body surface.  
6
- 7 23. A method for introducing or withdrawing an agent through a body  
8 surface, comprising the steps of:  
9 piercing the body surface with a plurality of protrusions extending  
10 from a first side of a member having a connecting medium capable of  
11 storing the agent therein or passing the agent therethrough on at least a  
12 portion of the first side;  
13 contacting the body surface with the connecting medium; and  
14 passing the agent through the body surface.
- 15 24. The method of Claim 23 wherein the passing step comprises:  
16 administering the agent by a method selected from the group  
17 consisting of electrotransport, passive delivery, osmosis, and pressure.  
18
- 19 25. The method of Claim 23 wherein the passing step comprises:  
20 sampling the agent by a method selected from the group consisting of  
21 reverse electrotransport, passive sampling, and osmosis.

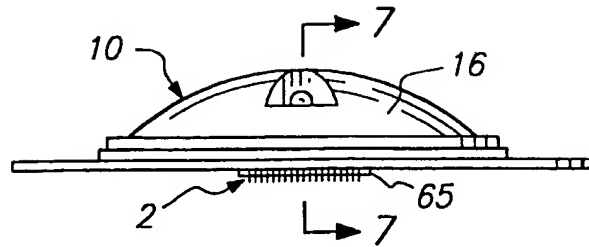




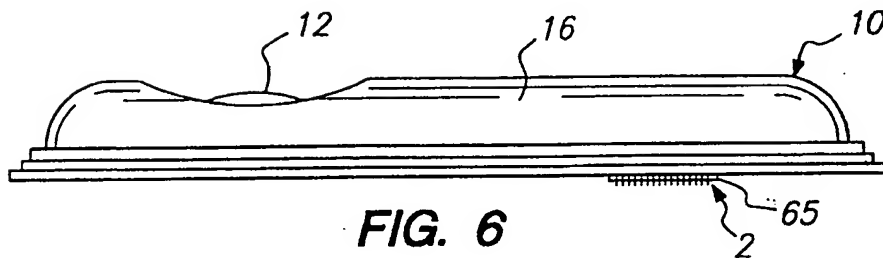
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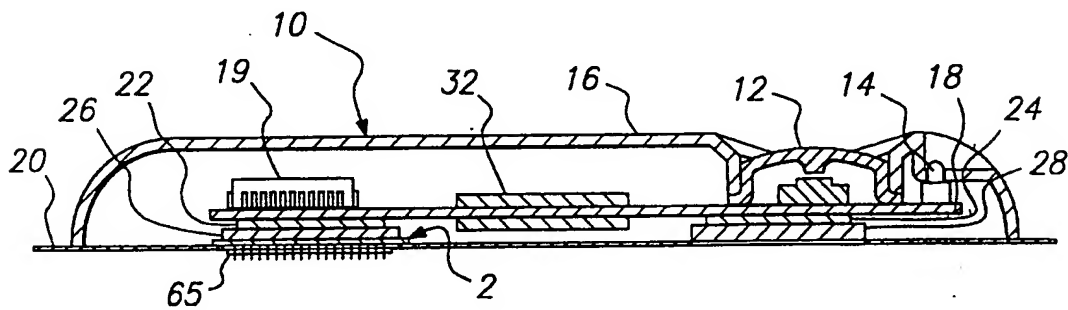
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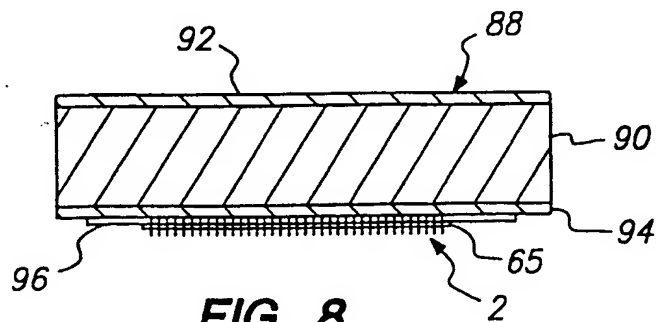
**FIG. 5**



**FIG. 6**

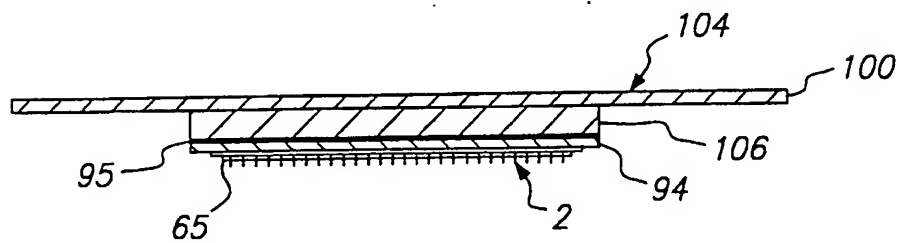
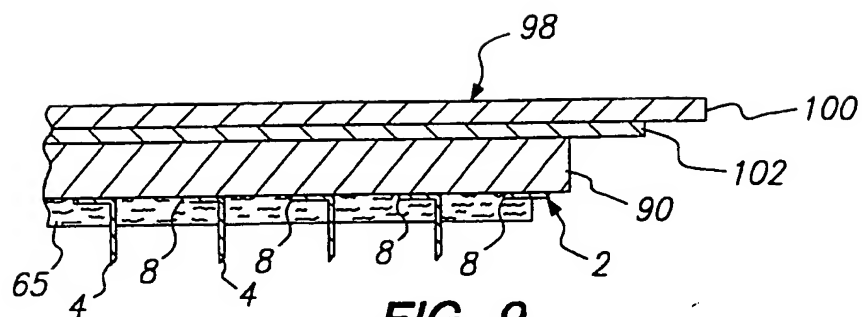


**FIG. 7**



**FIG. 8**

4/4



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/23274

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6    A61M37/00    A61N1/30    A61K9/70		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6    A61M    A61N    A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 37256 A (SILICON MICRODEVICES) 28 November 1996 see the whole document ---	1,2,12, 14,18
A	WO 96 17648 A (CIBA-GEIGY) 13 June 1996 see the whole document ---	1,2,14, 18
A	US 3 964 482 A (GERSTEL) 22 June 1976 cited in the application see abstract; figures ---	1,18
A	EP 0 429 842 A (KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY) 5 June 1991 cited in the application see claim 1; figures --- <div style="text-align: center;">-/--</div>	1,18
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-size: 1.2em;">9 April 1998</div>		Date of mailing of the international search report  <div style="text-align: center; font-size: 1.2em;">17.04.98</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-size: 1.2em;">Kousouretas, I</div>

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/23274

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	DE 195 25 607 A (BOEHRINGER INGELHEIM) 16 January 1997 see column 5, line 48 - column 6, line 2; figures -----	1,18

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/23274

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23-25  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/23274

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